# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-436

## MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data**
**NDA #21-436**

| | |
|---|---|
| **Sponsor:** | Otsuka/BMS |
| **Drug:** | Aripiprazole |
| **Indication:** | Schizophrenia |
| **Material Submitted:** | Response to 8-29-02 Approvable Letter |
| **Correspondence Date:** | September 18, 2002 |
| **Date Received:** | September 19, 2002 |

## I. Background

On 10-31-01, the sponsor submitted this NDA for the approval of aripiprazole in the treatment of schizophrenia.

The Office issued an approvable letter on 8-29-02. In summary, this letter indicated that, prior to approval, the sponsor would need to address several points, to include the following clinical issues:

1) follow-up laboratory data for 6 patients.
2) foreign regulatory update/foreign labeling.
3) world literature update.
4) submission of final printed labeling identical to that attached to the approvable letter.
5) safety update.
6) Phase 4 commitments to a) explore the efficacy of doses under 10 mg/day and b) provide data regarding longer-term efficacy (i.e., the results of study 138047).

This submission contains their response to the above.

## II. Clinical Data

### A. Follow-up Clinical Data on Six Patients

There were six patients who had abnormal laboratory findings at last visit with no follow-up:

1) 138001-33-102 (elevated SGOT).
2) 97201-36-18 (elevated SGOT).
3) 138001-7-458 (elevated CPK).

4) 97202-89-6 (low platelet count).
5) 138001-7-281 (low platelet count).
6) 97202-71-19 (low platelet count).

We had requested that the sponsor attempt to obtain follow-up data on these patients.

The sponsor re-contacted the involved investigator sites for these six patients. In most cases, there was no new information of consequence. Problems in data collection were mostly due to non-compliant patients, some of whom have been totally lost to follow-up (i.e., homeless). In one patient with an elevated CPK (138001-7-458), misplaced lab data was found and it showed diminishing CPK values at time of last measurement. In another case, the medical treatment facility had closed and no records were obtainable.

**B. Foreign Regulatory Update/Foreign Labeling**

Aripiprazole was approved in Mexico for the treatment of schizophrenia on 7-17-02. Marketing authorizations are pending in [redacted] The sponsor states that no negative regulatory actions have been taken in any country with respect to aripiprazole.

A review of the approved labeling from Mexico revealed no important clinical information that should be added to the U.S. labeling currently under consideration.

**C. World Literature Update**

The world's literature was updated by Julia Jui-mei Chuang from the sponsor's firm. Fifty-six articles were reviewed. No adverse safety findings were found. This fact was certified by Dr Joy Parris of Otsuka and Dr. Allan Safferman of BMS. A review of the three CV's of the above individuals was conducted and they are all satisfactory.

The databases searched with the appropriate search items included ADSI R&D Insight, MEDLINE, CAPLUS (Chemical Abstracts), EMBASE/EMBASE ALERTS, BIOSIS/Biological abstracts, SCISEARCH/Science Citation Index, DRUGU/Derwent Drug File, LIFESCI/Life Sciences Collection, TOXCENTER, IPA/International Pharmaceutical Abstracts, and

JICSTE/Japanese Information Center. The search interval was from January 1, 2002 to July 3, 2002.

Drs. Parris and Safferman each provided a warrant attesting to the above.

**D. Product Labeling**

The following comments are provided regarding the clinical sections of the sponsor's proposed labeling, found in volume 2 of this response:

CLINICAL PHARMACOLOGY/Clinical Studies
Efficacy information from the 52 week, active-controlled study should be removed since this trial, by design, cannot demonstrate the longer-term efficacy of aripiprazole in schizophrenia.

INDICATIONS AND USAGE
In accordance with the above comment, this section should indicate that the long-term efficacy of aripiprazole has not been established.

PRECAUTIONS/Use in Patients with Concomitant Illness
Placement of the statement regarding mortality in patients with psychosis associated with Alzheimer's dementia in this section (as opposed to WARNINGS) is not objectionable since the data do not clearly support a causal relationship between aripiprazole and these deaths.

ADVERSE REACTIONS/ECG Changes
The final paragraph, which describes QTc changes in study 99224, may be deleted as proposed by the sponsor given that the results in the 90mg dose group do appear to be driven by a single patient with highly variable QTc values. The small number of patients and high variability in ECG findings in this trial render these data difficult to interpret with reasonable certainty.

ADVERSE REACTIONS/Additional Findings Observed in Clinical Trials
The adverse event listing in this section was apparently constructed from a tabulation of ADR's, which excludes treatment-emergent events not deemed to be drug-related by investigators (Appendix 4.2.1 of this submission). The sponsor was requested to revise this table based on a

tabulation of all treatment-emergent adverse events (Appendix 4.2.2).[1]

DOSAGE AND ADMINISTRATION/Switching from Other Antipsychotics

The sponsor has added, as the first paragraph, some general guidance to prescribers regarding switching patients from other antipsychotics to aripiprazole. This language is very similar to that currently found in Seroquel labeling and is not objectionable.

However, they also propose to [redacted]

**E. Safety Update**

The sponsor has provided a Safety Update with a cut-off date of 6-30-02. The cut-off date for the 120-Day Safety Update, which was incorporated into the original clinical review, was 11-30-01.

Since the last update, 882 new patients received aripiprazole in non-Japanese Phase 2/3 studies as well as 59 new patients in non-Japanese Phase 1 trials and 55 new subjects in Japanese studies. As of 6-30-02, a total of 5,592 patients have been exposed to aripiprazole in non-Japanese Phase 2/3 studies.

There are no new safety data from short-term, placebo-controlled studies in patients with schizophrenia.

The review of this update focused on serious adverse events (SAE's), including deaths, in the non-Japanese Phase 2/3 studies. There were no new SAE's in the non-Japanese Phase 1 studies or in the Japanese studies.

**1. Deaths**

Among aripiprazole patients, there were 43 new deaths (39 in the Alzheimer's group) plus 2 deaths previously reported from studies that were still blinded as of the last update.

[1] In a 10-3-02 E-Mail to Charles Wolleben of BMS.

Deaths are enumerated by cause in Table 1 below. Line Listings and Narrative Summaries of new deaths were reviewed. The data were similar in every respect to those obtained from analysis of the prior studies and require no further comment.

**TABLE 2:**
**ENUMERATION OF ARIPIPRAZOLE DEATHS BY CAUSE (N)**
**APPROVABLE RESPONSE SAFETY UPDATE**

| Cause of Death | Study Pool | |
|---|---|---|
| | Schizophrenia/ Bipolar | Dementia |
| Pneumonia (Aspiration) | - | 1 |
| Pneumonia (Other/Unspecified) | - | 7 |
| Myocardial Infarction | - | 1 |
| Heart Failure | 1 | 4 |
| Sepsis | - | 6 |
| Cachexia | - | 2 |
| Cardiac Arrest | 1 | 8 |
| Pulmonary Embolism | 1 | 1 |
| Cancer | 2 | - |
| Stroke | - | 4 |
| Respiratory Distress Syndrome | - | 3 |
| End-Stage Dementia | - | 1 |
| Intestinal Obstruction | - | 1 |
| Diabetes | - | 1 |
| **TOTAL** | **5** | **40** |

Exposure-adjusted mortality rates (per 1000 PY's) for the cumulative database by diagnostic group are as follows and are similar to those observed in the previously reviewed safety database: 8.5 in the schizophrenia studies, 7.9 in the bipolar mania studies, and 220 in the dementia studies.

**2. All Serious Adverse Events**

There were 264 new SAE's in the non-Japanese Phase 2/3 studies. Line listings of all new SAE's were reviewed (Appendix 4.4A of the safety update). Narrative summaries of events that possibly represented clinically significant and previously unrecognized events were reviewed in detail.

Overall, the pattern of SAE's followed that of the previously reviewed database. No important, new SAE's were found.

**F. Phase 4 Commitments**

The sponsor agreed to all requested Phase 4 commitments, to include an exploration of the efficacy of doses under 10 mg/day and submission of data from study 138047 regarding the longer-term efficacy of aripiprazole in schizophrenia.

**III. Conclusions and Recommendations**

This submission is a full and adequate response to the clinical issues raised in our approvable letter. There is no clinical information in this submission that would change our previous conclusions about the approvability of aripiprazole.

From a clinical perspective, this application may be approved when agreement is reached on product labeling.

/S/

Gregory M. Dubitsky, M.D.
October 4, 2002

/S/

Robert Harris, M.D., Ph.D.
October 4, 2002

cc: NDA #21-436
HFD-120 (Div. File)
HFD-120/GDubitsky
/RHarris
/TLaughren
/SHardeman

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Greg Dubitsky
10/4/02 04:47:00 PM
MEDICAL OFFICER

Robert D. Harris
10/7/02 02:19:20 PM
MEDICAL OFFICER

Thomas Laughren
11/7/02 05:22:47 PM
MEDICAL OFFICER
We have reached agreement on final labeling as of 11-7-02, and I agree that we can now approve this NDA.--TPL

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# Demographic Worksheet

**lication Information** *(Enter all identifying information for the submission pertaining to this summary)*

**NDA Number:** 21-436 **Submission Type:** N/A (pilot) **Serial Number:** N/A (pilot)

**Populations Included In Application** *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

| Category | | Number Exposed To Study Drug | | Number Exposed To Study Drug | | Number Exposed To Study Drug |
|---|---|---|---|---|---|---|
| Gender | Males | 699 | All Females | 227 | Females >50 | 54 |
| Age: | 0-≤1 Mo. | 0 | >1 Mo.-≤2Year | 0 | >2-≤12 | 0 |
| | 12-16 | 0 | 17-64 | 918 | ≥65 | 8 |
| Race: | White | 506 | Black | 283 | Asian | 21 |
| | Other | 116 | | | | |

**Gender-Based Analyses** *(Please provide information for each category listed below.)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was gender-based analysis included in labeling? Yes | No |
|---|---|---|---|---|---|---|
| Efficacy | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |
| Safety | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

**Age-Based Analyses** *(Please provide information for each category listed below)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was age-based analysis included in labeling? Yes | No |
|---|---|---|---|---|---|---|
| Efficacy | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |
| Safety | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

**Race-Based Analyses** *(Please provide information for each category listed below)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was race-based analysis included in labeling? Yes | No |
|---|---|---|---|---|---|---|
| Efficacy | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |
| Safety | ☒ Yes | ☐ No | ☐ Inadequate #'s | ☐ Disease Absent | ☒ | ☐ |

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

**Comment:**

**A PK study in 19 patients with hepatic impairment was done. A PK study in 6 patients with severe renal impairment was done. There were no modifications to the Dosage and Administration section of product labeling based on the results of these two studies.**

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Greg Dubitsky
10/7/02 02:11:45 PM

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# REVIEW AND EVALUATION OF CLINICAL DATA

**Application Information**

| | |
|---|---|
| NDA#: | 21-436 |
| Sponsor: | Otsuka/Bristol-Myers Squibb |
| Due Date: | August 31, 2002 |

**Drug Name:**

| | |
|---|---|
| Generic Name: | Aripiprazole (OPC-14597) |
| Trade Name: | [redacted] |

**Drug Categorization:**

| | |
|---|---|
| Pharmacological Class: | $D_2$ partial agonist |
| Proposed Indication: | Schizophrenia |
| Dosage Forms: | 10mg, 15mg, 30mg tablets |
| Route: | Oral |

**Review Information**

| | |
|---|---|
| Clinical Reviewers: | Gregory M. Dubitsky, M.D.<br>Robert Harris, M.D., Ph.D. |
| Completion Date: | June 12, 2002 |

# NDA 21-436
# ARIPIPRAZOLE TABLETS FOR SCHIZOPHRENIA
# TABLE OF CONTENTS

# EXECUTIVE SUMMARY

## I. Recommendations

### A. Recommendation on Approvability

It is recommended that aripiprazole tablets be approved for the treatment of _____ adult patients with schizophrenia.

### B. Recommendations for Phase 4 Studies

It is recommended that the following Phase 4 commitments be requested from the sponsor:

1) an adequate and well-controlled study of aripiprazole in the treatment of children and adolescents with schizophrenia.

2) a study to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia. The recently completed Study 138047 may be adequately designed to address longer-term efficacy (see section VI.C.4) and the study report may be submitted as an efficacy supplement to satisfy this commitment.

## II. Summary of Clinical Findings

### A. Brief Overview of the Clinical Program

The aripiprazole clinical program consisted of 35 Phase 1 and 36 Phase 2/3 studies conducted worldwide (excluding Japan) as of 11-30-01. The Phase 2/3 studies have been conducted in patients with schizophrenia and schizoaffective disorder, mania associated with bipolar disorder, and psychosis associated with Alzheimer's disease. A total of 4710 patients have received aripiprazole in the non-Japanese Phase 2/3 studies and, of these, 926 were patients with schizophrenia or schizoaffective disorder who received aripiprazole in short-term, placebo-controlled studies.

In addition, as of 10-31-01, 9 Phase 1 studies and 10 Phase 2/3 studies in schizophrenia have been conducted with aripiprazole in Japan. A total of 769 patients received aripiprazole in the Japanese Phase 2/3 trials. Japanese

studies are considered separately for reasons described in section IV.A. below.

**B. Efficacy**

The sponsor conducted five short-term, multicenter, randomized, double-blind, placebo-controlled trials in hospitalized patients to demonstrate efficacy in schizophrenia. The results of these studies are summarized below.[1]

Study 93202 was a 4-week trial in patients with DSM-III-R schizophrenia in acute relapse. Altogether, 103 patients were randomized to aripiprazole, haloperidol, or placebo. The active drugs were titrated to target doses of aripiprazole 30 mg/day or haloperidol 20 mg/day within the first 2 weeks of dosing. There were two primary efficacy variables: change from baseline in the BPRS total score and the percentage of patients with at least one point improvement on the CGI-severity scale. Aripiprazole demonstrated borderline statistical superiority on the latter variable only. Haloperidol was superior on both variables. This was a negative study for aripiprazole.

Study 94202 was a 4-week study in patients with DSM-IV schizophrenia in acute relapse. This study randomized 307 patients to one of three fixed doses of aripiprazole (2, 10, or 30 mg/day), haloperidol 10 mg/day, or placebo. One site was excluded from the efficacy analysis because of Agency disqualification of the investigator (Dr. Borison). All target doses were attained by day 3. There were two primary efficacy variables: change from baseline in the BPRS core score (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content items) and CGI rating of improvement at last visit. Aripiprazole 30mg was statistically superior to placebo only on the latter variable; the 2mg and 10mg doses showed no superiority. Haloperidol was superior only on the former variable. This was a failed study since neither aripiprazole nor the active comparator, haloperidol, demonstrated efficacy.

Study 97201 was a 4-week study in patients with DSM-IV schizophrenia or schizoaffective disorder. This trial randomized a total of 414 patients to fixed doses of

[1] The LOCF dataset was considered to be primary.

aripiprazole (15 or 30 mg/day), haloperidol 10 mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment. There were three primary efficacy variables: changes from baseline in the PANSS total score, the PANSS positive subscale, and the CGI-severity score. After multiple comparison adjustment, both doses of aripiprazole were found to be statistically superior to placebo. There appeared to be no therapeutic advantage of the 30mg dose over the 15mg dose. The therapeutic response was similar for both the schizophrenia and schizoaffective subsets of the study population.

Study 97202 was a 4-week study in patients with DSM-IV schizophrenia or schizoaffective disorder. This trial randomized a total of 404 patients to fixed doses of aripiprazole (20 or 30 mg/day), risperidone 6 mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment. There were three primary efficacy variables: changes from baseline in the PANSS total score, the PANSS positive subscale, and the CGI-severity score. After multiple comparison adjustment, both doses of aripiprazole were found to be statistically superior to placebo. There appeared to be no therapeutic advantage of the 30mg dose over the 15mg dose. The therapeutic response was similar for both the schizophrenia and schizoaffective subsets of the study population.

Study 138001 was a 6-week trial in patients with DSM-IV schizophrenia in acute relapse. A total of 420 patients were randomized to one of three fixed doses of aripiprazole (10, 15, or 20 mg/day) or placebo. Aripiprazole was given as a full fixed dose from the first day of treatment. There was one primary efficacy variable: mean change from baseline in the PANSS total score. A protocol amendment provided for two key secondary variables: mean changes from baseline in the PANSS-derived BPRS Core Score and the PANSS Negative Subscale score. All three aripiprazole doses were statistically superior to placebo on the primary variable and both key secondary variables. There was no apparent advantage of the 15 and 20mg doses over the 10mg dose.

In sum, three of the five short-term studies demonstrated the efficacy of aripiprazole over a dose range 10 to 30 mg/day. Of the two remaining studies, one was negative and one failed.

## C. Safety

The primary aripiprazole safety database consisted of the pool of all non-Japanese Phase 2/3 studies. As of the cut-off date for the 120-Day Safety Update (11-30-01), 4710 patients had received aripiprazole in this pool of studies. This represents 2656.3 patient-years of exposure. Among these 4710 patients, 3561 participated in schizophrenia trials, 645 patients in bipolar mania studies, and 504 in dementia trials.

Other sources of safety data included Japanese Phase 2/3 studies, in which 769 patients received aripiprazole as of 10-31-01, and all Phase 1 studies. The sponsor also conducted a literature search to identify any other important safety findings.

Aripiprazole has not yet been marketed in any foreign country.

The major safety findings from the NDA safety review are summarized below.

In short-term, placebo-controlled schizophrenia trials, no adverse events met the commonly used criteria for common, drug-related events (≥5% incidence for drug and at least twice the placebo incidence). Somnolence did appear to be dose-related, occurring in 15.3% of patients treated with aripiprazole 30 mg/day. The incidence of extrapyramidal symptoms with aripiprazole approximated that with placebo except for akathisia (10.0% for aripiprazole vs. 6.8% for placebo).

The occurrence of orthostatic hypotension was not much higher than for placebo (14.0% vs. 11.9%).

At doses to 30 mg/day, there was no evidence of $QT_c$ interval prolongation. However, in a special study that explored doses to 90 mg/day, there was substantial prolongation of $QT_c$ at 75 and 90 mg/day (27 and 24 msec median changes from baseline to maximum value when QT was corrected by $QT_c = QT/RR^{0.37}$).

In a 26-week study designed to compare weight gain between aripiprazole and olanzapine, aripiprazole was associated with significant weight gain in 13% of patients compared to 33% of olanzapine-treated patients.

Special safety analyses did not suggest that aripiprazole treatment was associated with disturbance of glucose or lipid metabolism or elevated prolactin levels.

A finding of gallsand and gallstones in preclinical studies with monkeys prompted a concern that aripiprazole may be associated with gallbladder disease in humans. Another special safety analysis of Phase 2/3 data showed that the risk of gallbladder disease in patients who received aripiprazole was not higher than expected.

There were three safety findings among elderly patients with dementia who received aripiprazole which deserve special attention: mortality, pneumonia, and somnolence. Although this is not the target population for this NDA, aripiprazole is likely to be used off-label if approved and it would be prudent to advise prescribers of these findings, which are summarized in more detail in section VII.E of this review.

**D. Dosing**

The three positive efficacy trials utilized four fixed daily doses of aripiprazole: 10mg, 15mg, 20mg, and 30mg. Only one of these trials used a 10mg dose, study 138001. In this study, 10mg was efficacious. Thus, there is less evidence supporting the efficacy of the 10mg dose compared to each of the three higher doses, for which efficacy was shown in two studies.

In each of these three studies, there was no clear advantage of the higher dose(s) over the low dose.

In these studies, aripiprazole was administered as a full fixed dose once daily from the first day of treatment. In studies 97201 and 97202, aripiprazole was taken in the morning; in study 138001, aripiprazole was taken at about the same time each day but the time of day was not specified.

Steady-state blood levels are achieved within 14 days.

Based on the above considerations, it seems reasonable to recommend an adult starting dose of 15mg given once daily. If needed to achieve an acceptable therapeutic response,

the dose could be increased in increments of 5-10 mg/day at intervals of at least 2 weeks to a maximum of 30 mg/day.

Study 98215 examined three regimens for switching patients on other antipsychotics to aripiprazole (see section VII.B.9.d):

1) immediate initiation of 30 mg/day oral aripiprazole with simultaneous immediate discontinuation of the current antipsychotic (N=104),
2) immediate initiation of 30 mg/day oral aripiprazole while tapering off the current antipsychotic (over a 2-week period) (N=104), or
3) titrating up initiation of oral aripiprazole over a 2-week period (from 10 mg/day to 30 mg/day) while tapering off the current antipsychotic monotherapy over the same 2-week period, then maintaining 30 mg/day oral aripiprazole dosing (N=103).

This study showed that the overall efficacy, safety, and tolerability profiles were generally similar across the three treatment switching strategies.

**E. Special Populations**

The safety and efficacy of aripiprazole in pediatric patients have not been established.

Pharmacokinetic studies have demonstrated no major differences in the pharmacokinetics of aripiprazole based on age, gender, race, smoking status, hepatic or renal impairment, or CYP2D6 metabolizer status.[2]



[2] This information is based on the Application Summary. These studies are currently pending review by the FDA biopharmaceutics reviewer, Dr. Hong Zhao.

# CLINICAL REVIEW

## I. Introduction and Background

### A. Role in the Treatment Armamentarium

Aripiprazole is an atypical antipsychotic developed for the treatment of psychosis in patients with schizophrenia. It differs from currently marketed atypical antipsychotics in that it is a partial agonist at dopamine $D_2$ receptors, i.e., it acts as an agonist in an animal model of dopaminergic hypoactivity and as an antagonist in animal models of dopaminergic hyperactivity. Thus, it belongs to a new class of antipsychotics called dopamine system stabilizers (or DSS's). The exact molecular mechanism for this partial agonism remains obscure. It is hypothesized that this action allows sufficient dopamine activity in the nigrostriatal pathways to prevent motor side effects while reducing dopamine sufficiently in mesolimbic pathways to produce antipsychotic effects.[3]

Additionally, aripiprazole possesses 5-$HT_{1A}$ partial agonist activity and 5-$HT_{2A/2C}$ antagonist activity, which are thought to play some role in producing antipsychotic effects.

### B. Safety Findings with Related Compounds

Aripiprazole is most closely related pharmacologically to the atypical antipsychotics, which have been associated with different safety issues to varying degrees. Atypical agents are listed in **Table I-1** along with the important safety concerns associated with each.



[3] Stahl SM. Dopamine System Stabilizers, Aripiprazole, and the Next Generation of Antipsychotics, Part 1. J Clin Psychiatry 2001;62:841-2.

| TABLE I-1<br>MAJOR SAFETY CONCERNS WITH OTHER ATYPICAL ANTIPSYCHOTICS | |
|---|---|
| **Clozapine** | Agranulocytosis<br>Seizures<br>Myocarditis<br>Orthostatic hypotension<br>Hyperglycemia<br>Weight gain |
| **Risperidone** | Prolactin elevation<br>Orthostatic hypotension<br>Weight gain |
| **Olanzapine** | Orthostatic hypotension<br>Weight gain<br>Hyperglycemia |
| **Quetiapine** | Orthostatic hypotension<br>Weight gain<br>? Cataracts |
| **Ziprasidone** | QT interval prolongation |
| **Sertindole (not marketed)** | QT interval prolongation<br>Sudden death |

**C. Administrative History**

OPC-14597 (later named aripiprazole) was discovered by Otsuka Pharmaceutical Company in 1988 and was first administered to humans in 1990 in Japan. An IND application was submitted to the Agency on 6-10-93 to initiate studies in the U.S.

On 7-6-93, there was an internal meeting of the review team and, based on that discussion, Otsuka was informed that they could proceed with investigations under

Following completion of several studies under this IND, representatives of Otsuka met with the FDA review team on 2-19-97 for an End-of-Phase 2 meeting. Important clinical issues discussed at this meeting included the following:

- safety exposure should include 400-600 patients exposed for 6 months or longer.
- an evaluation of time to therapeutic effect would have to entail frequent measurements, examination of the distribution of times to onset, and a consensus on how to

define response, which could not be based on a total score of a number of diverse items.

- translation of Japanese CRF's would not be necessary but we would need English-based tabulated safety data and narrative summaries for serious adverse events.
- all studies capable of demonstrating the efficacy of aripiprazole would have to be submitted regardless of outcome.
- comparative safety claims would have to be based on either: 1) a comparison of the highest aripiprazole dose with the lowest dose of comparator after showing that the dose-response curve for aripiprazole was not inverted U-shaped OR 2) a trial with several fixed dose arms for each drug (e.g., a seven-arm study with 3 dose groups for each drug plus placebo).

A co-development agreement was signed between Otsuka and Bristol-Myers Squibb (BMS) in September 1999. As a result, it was decided to expand the development plan for aripiprazole to pursue additional indications beyond schizophrenia (see below).

Another meeting was held between the Division review team and representatives of Otsuka and Bristol-Myers Squibb on 2-2-00 to discuss the co-sponsors' expanded development program for aripiprazole. Specifically, the co-sponsors had elected to seek approval for the following indications: schizophrenia, [redacted]

- the program for [redacted] as described, was adequate in design to support approval.
- [redacted]
- the Division would require expert input before providing guidance on the indications of psychosis associated with [redacted] (This would be the subject of a 3-9-00 advisory committee meeting.)
- the indication of [redacted] is problematic since it is unclear whether this represents a psychiatric disease and outcome measures are ill-defined.

• the safety profile and proposed indications for aripiprazole do not qualify for priority review status.

A pre-NDA meeting was held with the sponsors on 7-2-01 to review plans for an NDA to be submitted in October 2001. This NDA would seek approval for the treatment of [redacted] schizophrenia and [redacted]. Important clinical issues discussed at this meeting included:

• data from fixed dose studies in schizophrenia suggested efficacy over a wide dose range (2-30 mg/day). After discussion of the data, it seemed most reasonable to recommend a target dose of 15 mg/day in labeling, while adding that doses to 30 mg/day are safe and effective but have not been shown to demonstrate an advantage over lower doses.

• probable labeling of the finding of gallsand and gallstones in monkeys given lack of an apparent signal in humans.

• potential problems with comparative safety claims in labeling.

• a precedent for describing effects on positive and negative symptoms of schizophrenia in labeling under Clinical Trials (but not Indications) even though such measures may not have been prespecified as primary variables.

• the schizophrenia studies would not support a second indication of [redacted] despite the fact that some of the patients in two of the trials were diagnosed with [redacted] (This fact might be mentioned under Clinical Trials, however.)

• pediatric PK data would not be incorporated into labeling until after approval in this population.

The two key studies in [redacted] were completed in July 2001. Subsequent to completion, it was discovered that one of these studies (138007) failed to demonstrate efficacy on the primary efficacy measure. Thus, the sponsor informed us on 9-24-01 that the upcoming NDA submission would not include the [redacted] but only the schizophrenia indication.

This NDA was submitted and received on 10-31-01. It was decided to file the NDA at a meeting on 12-18-01.

A 120-Day Safety Update to the NDA was submitted on 2-27-02.

**D. Proposed Instructions for Use**

Aripiprazole is proposed for use in the treatment of schizophrenia in adults.

The recommended starting dose is 15 mg/day administered once daily without regard to meals. Daily doses of 20 and 30 mg were also safe and efficacious in clinical trials but there appeared to be no therapeutic advantage, on average, of these doses over 15 mg/day. Safety and efficacy in pediatric patients has not been established.

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment.

The efficacy of aripiprazole has not been evaluated in adequate, well-controlled studies beyond 6 weeks in duration. There is no body of evidence to suggest how long a patient should be treated with aripiprazole. Patients should be maintained on the dose to which they respond and should be periodically reassessed to determine the need for maintenance treatment.

Patients may be switched from other antipsychotics to aripiprazole by any of the following three methods: 1) immediate discontinuation of the current medication and immediate initiation of aripiprazole, 2) immediate initiation of aripiprazole while tapering the current medication over a two-week period, or 3) upward titration of aripiprazole over a two-week period while simultaneously tapering the current medication over the same two-week period.

**E. Foreign Marketing**

Aripiprazole has not been marketed in any foreign country.

**II. Clinically Relevant Findings from Other Disciplines and from Consultants**

**A. Statistical Review and Evaluation**

The Statistical Review and Evaluation is complete and is pending supervisory sign-off as of the date of this review.

Verbal consultation with the statistical reviewer, Dr. Yeh-Fong Chen, indicates agreement that studies 97201, 97202, and 138001 provide sufficient evidence of the efficacy of aripiprazole in the treatment of schizophrenia.

**B. Biopharmaceutics**

The biopharmaceutics review has not been completed as of the date of this review.

**C. Pharmacology/Toxicology**

The pharmacology/toxicology review has not been completed as of the date of this review.

**D. Chemistry**

The chemistry review was almost complete as of the date of this review. Verbal consultation with the chemistry reviewer, Dr. Sherita McLamore, indicated no major deficiencies or problems from a CMC standpoint.

**E. DMETS Assessment of Tradename**

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety evaluated the sponsor's initially proposed tradename for aripiprazole (Abilitat). They found it to be unacceptable because it could be mistaken with other marketed drugs (e.g., Adalat). In a 10-18-01 letter from the Division, the sponsor was notified of this finding and requested to propose an alternative tradename. Subsequently, the sponsor proposed the name ——— in a 4-24-02 submission. This proposal is currently under evaluation by DMETS.

**F. DSI Clinical Site Inspections**

The Division of Scientific Investigations (DSI) inspected a total of four clinical sites from studies 97201, 97202, and 138001. All inspections were classified as either NAI (no deviations from regulations) or VAI (minor deviations from regulations) according to a 5-28-02 report from DSI. All data were considered acceptable.

## III. Human Pharmacokinetics and Pharmacodynamics

### A. Pharmacodynamics

Aripiprazole is a partial agonist at dopamine $D_2$ receptors, that is, it acts as an agonist in an animal model of dopaminergic hypoactivity and as an antagonist in animal models of dopaminergic hyperactivity. It exhibits high to moderate affinity for dopamine $D_3$, histamine $H_1$, and alpha-1 adrenergic receptors as well as for multiple serotonin receptor subtypes (5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_6$, and 5-$HT_7$). It has low affinity for muscarinic receptors.

In a PET study (Study 94201) of aripiprazole binding to dopamine $D_2$ receptors in the brains of healthy male volunteers, it was demonstrated that aripiprazole binds to human $D_2$ receptors in a dose-related fashion up to 10 mg/day at steady-state. At 10 mg/day, binding was approximately 85%. At the next highest dose studied, 30 mg/day, receptor occupancy was in the range 80-95%.

### B. Pharmacokinetics[4]

#### 1. ADME

The absolute oral bioavailability of aripiprazole was 87% in healthy subjects. This indicates nearly complete absorption and little first-pass metabolism. Steady-state Cmax and AUC increase linearly and proportionally over the dose range 5-30 mg/day in healthy volunteers. In schizophrenic patients, aripiprazole pharmacokinetics appear to be linear at doses in the range 30-90 mg/day. Cmax occurs at 3-5 hours post-dose at steady-state. Administration of a high-fat meal had no effect on the pharmacokinetics of aripiprazole or its active metabolite. Activated charcoal decreased the concentrations of aripiprazole and its active metabolite by 54% each, suggesting that charcoal may be an effective intervention for overdose.

The steady-state volume of distribution after intravenous administration was 4.94 L/kg, suggesting extensive tissue distribution. Plasma protein binding was greater than 99%.

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[4] The data presented in this section are from section 7 (Clinical Pharmacology) of the Application Summary.

Aripiprazole is metabolized by three pathways: dehydrogenation, N-dealkylation, and hydroxylation. Dehydrogenation produces the active metabolite, OPC-14857, which is then further metabolized by N-dealkylation and hydroxylation. OPC-14857 has comparable binding affinity to $D_2$ and $D_3$ receptors and the AUC ratio of this metabolite to parent drug is 0.39. Thus, it likely contributes to the pharmacological activity of aripiprazole. The AUC ratios for all other metabolites to parent drug were very low (<0.002), making it unlikely that they contribute to the pharmacological effect of the drug.

The P450 isozymes responsible for aripiprazole metabolism are CYP3A4 (catalyzes all three pathways) and CYP2D6 (catalyzes dehydrogenation and hydroxylation). The isozymes CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2E1 do not appear to be involved in aripiprazole metabolism.

Aripiprazole is eliminated primarily via metabolism. Its metabolites are eliminated by both the renal and biliary routes in humans. The mean elimination half-life of aripiprazole is 75 hours (range 31-146 hours). With daily administration, steady-state concentrations of aripiprazole and its active metabolite OPC-14857 are achieved after approximately two weeks. Consistent with the long half-life, the steady-state accumulation index is 5.

**2. Pharmacokinetics in Special Populations**

Phase 1 trials and the results of a population pharmacokinetic analysis of Phase 2 and Phase 3 studies in adults showed no major differences in the pharmacokinetics of aripiprazole based on age, gender, race, or smoking status.

After administration of a single 15mg dose, there were no important differences in aripiprazole pharmacokinetics between healthy subjects and subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).

Also, following a single 15mg dose in healthy subjects and in subjects with severe renal impairment (creatinine clearance <30mL/min), there were no differences in the pharmacokinetics of aripiprazole and OPC-14857 between the two groups.

After a single 10mg dose of aripiprazole in CYP2D6 poor metabolizers (PM) and extensive metabolizers (EM), plasma concentrations of the active metabolite OPC-14857 were decreased 37% in the PM vs. the EM subjects with an increase in parent drug concentrations that was complementary to the decrease in the metabolite. Since aripiprazole and OPC-14857 have comparable $D_2$ receptor affinities and similar protein binding, CYP2D6 genotype or phenotype is not expected to affect the safety or efficacy of aripiprazole.

**3. Assessment of Drug-Drug Interactions**

**a. Effects of Other Drugs on Aripiprazole**

Ketoconazole, a potent CYP3A4 inhibitor, decreased the clearance of a single 15mg dose of aripiprazole by 38% and increased plasma levels of OPC-14857 by 77%.

Quinidine, a potent CYP2D6 inhibitor, decreased the clearance of a single 10mg dose of aripiprazole by about 50% and decreased plasma levels of OPC-14857 by 34%.

Co-administration of carbamazepine 200mg BID with aripiprazole 30 mg/day in patients with schizophrenia or schizoaffective disorder increased the clearance of aripiprazole.

Co-administration of lithium (1200-1800 mg/day) for 21 days with aripiprazole 30 mg/day in patients with schizophrenia or schizoaffective disorder had no clinically significant effect on the pharmacokinetics of aripiprazole or OPC-14857. No effect of aripiprazole on lithium pharmacokinetics is expected.

Administration of valproate (350-1500 mg/day) for 21 days with aripiprazole 30 mg/day to patients with schizophrenia or schizoaffective disorder had no clinically significant effect on the pharmacokinetics of aripiprazole.

There was no evidence of EEG findings suggestive of epileptiform activity, encephalopathy, or other pathological EEG rhythms with co-administration of lithium, valproate, or carbamazepine with aripiprazole.

**b. Effects of Aripiprazole on Other Drugs**

Based on in_vitro data, aripiprazole is not expected to significantly inhibit the in vivo activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 at clinically relevant concentrations.

Various studies examined the effect of aripiprazole at doses of 10-30 mg/day given for 14 days on substrates for CYP2D6 (dextromethorphan O-dealkylation), CYP3A4 (dextromethorphan N-demethylation), CYP2C9 (R and S warfarin), and CYP2C19 (omeprazole). No effects were observed in these studies.

## IV. Description of Clinical Data Sources

Note: This review includes the clinical data contained in the 120-Day Safety Update to this NDA, which was submitted on 2-27-02.

### A. Primary Development Program

Trials in the development program for aripiprazole were conducted in a number of locations worldwide, to include North America, Europe, and Japan. The Japanese studies were considered separately from trials conducted elsewhere for several reasons: 1) they were conducted on a narrow ethnic population, which limits generalizability; 2) there were differences in study drug tablet strength and formulation between the Japanese studies and other aripiprazole studies, 3) a different adverse event dictionary was used to code adverse events in the Japanese studies (J-ART versus modified COSTART in the other aripiprazole trials). Additionally, there was a difference in the cut-off dates for clinical safety data between the Japanese and non-Japanese study pools. Thus, for purposes of this review, the Japanese studies will constitute a separate study pool for safety data analysis.

A listing of all studies in the sponsor's development program is presented in **Appendix IV-1**.

## 1. Non-Japanese Studies

### a. Patient Enumeration by Study Type

The cut-off date for safety data from the non-Japanese studies was 11-30-01.[5] At that timepoint, a total of 5634 subjects and patients had been exposed to aripiprazole tablets in non-Japanese studies.

Of these, 924 participated in 35 Phase 1 studies. These studies involved both healthy volunteers and patients with either schizophrenia or schizoaffective disorder.

Another 4710 patients participated in Phase 2/3 studies. The Phase 2/3 studies were of various designs in different indications: short-term placebo-controlled trials in schizophrenia, longer-term controlled studies in schizophrenia; short-term placebo-controlled trials in bipolar mania; a placebo-controlled study in Alzheimer's dementia; ongoing studies that remained blinded as of 11-30-01, and open-label studies or study phases that were ongoing as of 11-30-01; and completed special studies (2 high-dose pilot studies, 1 open-label treatment switching study, and 1 open-label pilot study in dementia).

Among the 4710 patients in Phase 2/3 trials, 3561 participated in schizophrenia trials, 645 patients in bipolar mania studies, and 504 in dementia trials.

A total of 926 patients received aripiprazole in 5 short-term, placebo-controlled schizophrenia studies within the non-Japanese Phase 2/3 study pool.

Subjects and patients in all non-Japanese trials are enumerated by study type in **Appendix IV-2**.

### b. Demographic Characteristics

Demographic characteristics for aripiprazole-treated patients in the non-Japanese Phase 2/3 study pool are presented in **Appendix IV-3**. There were some noteworthy demographic differences between the patient groups studied for these indications:

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[5] Except for the Phase 1 study 138065, for which the cut-off date was 1-15-02.

• As expected, patients in dementia studies were considerably older than patients in the schizophrenia and bipolar studies (mean ages of 81.7, 38.7, and 40.1 years, respectively). Most dementia study patients (97%) were at least 65 years old.
• 75% of dementia patients and 56% of bipolar manic patients were female; only 33% of schizophrenia patients were female.
• 89% of dementia patients were white whereas only 74% of bipolar mania and 69% of schizophrenia patients were white.

Demographic features of control group (placebo, risperidone, olanzapine, and haloperidol) patients are presented in **Appendix IV-4**. In the placebo group, 116 patients were age 65 or older; in the other groups, there were very few elderly patients.

Demographic characteristics for patients in the 5 short-term placebo-controlled studies in schizophrenia are presented in **Appendix IV-5**. Aripiprazole patients were predominantly men (75%). The majority (85%) of the patients were between 18 and 50 years of age with the mean age ranging from 38.6 to 39.1 years, and approximately 1% of the patients were 65 years of age or older. Racially, 55% were white and 31% were black. Treatment groups were comparable with regard to age, gender, and race.

Two Phase III short-term placebo-controlled trials (31-97-201 and 31-97-202) included patients with a diagnosis of schizoaffective disorder; this population constituted approximately 30% of the overall patient population in each of these studies (132 of 414 randomized patients in 31-97-201 and 115 of 404 randomized patients in 31-97-202).

**c. Extent of Exposure**

Patient exposure by mean dose and duration of treatment with aripiprazole is summarized in **Appendix IV-6** for the non-Japanese Phase 2/3 study pool. A total of 1513 patients in this study pool received aripiprazole for 6 months or longer, 902 patients received aripiprazole for at least one year (≥360 days), and 421 patients continued aripiprazole treatment for at least 2 years (≥720 days). However, almost all of this longer-term use was in patients with schizophrenia; only 20 dementia patients and no

bipolar mania patients received aripiprazole for at least a year.

Overall, over half of these patients (N=2544) received a mean dose of aripiprazole in the range >25 and ≤32.5 mg/day.

For the non-Japanese Phase 2/3 study pool, exposure in patient-years by treatment was as follows:

| Treatment | N | Patient-Years |
|---|---|---|
| Aripiprazole | 4710 | 2656.3 |
| Placebo | 928 | 85.8 |
| Haloperidol | 673 | 207.3 |
| Olanzapine | 393 | 126.9 |
| Risperidone | 99 | 6.0 |

The 5 short-term placebo-controlled studies in schizophrenia were 4 or 6 weeks in duration. Three included a haloperidol control and one included a risperidone control. Patient exposure to aripiprazole in these short-term trials is summarized in **Appendix IV-7**. In the fixed dose studies, 892 patients received doses that ranged from 2-30 mg/day. In one flexible dose trial, 34 patients were dosed in the range 5-30 mg/day. At least 4 weeks of aripiprazole treatment was received by 181 patients in these trials.

In this short-term study pool, patient-years of exposure by treatment was as follows:

| Treatment | N | Patient-Years |
|---|---|---|
| Aripiprazole | 926 | 59.52 |
| Placebo | 413 | 24.19 |
| Haloperidol | 200 | 11.44 |
| Risperidone | 99 | 5.96 |

**2. Japanese Studies**

The cut-off date for clinical safety data from the Japanese studies was 10-31-01. As of that date, 132 subjects received aripiprazole in 9 Phase 1 trials and 769 patients received aripiprazole in 10 Phase 2/3 studies.

A much smaller number of patients received other study drugs in these studies: 131 received haloperidol, 121 received mosapramine, and only 8 received placebo.

Information regarding demographic characteristics and extent of aripiprazole exposure was not provided for these 19 trials.

**B. Other Sources of Clinical Data**

**1. Non-IND Studies**

No non-IND studies are reported.

**2. Published Literature**

The methodology for the literature search, which was conducted by both Otsuka and Bristol-Myers Squibb (BMS), was as follows:

Otsuka performed searches in Japan at Otsuka's Office of Scientific Information using these search terms: ARIPIPRAZOLE, OPC-14597, OPC141597, OPC-31, OPC31, ABILITAT, 156680-99-8 (CAS Registry #). Databases and dates searched for online bibliographic references available as of January 7, 2002 were: DERWENT DRUG FILE (1983-January 7, 2002), EMBASE/EMBASE Alert (1974 to January 7, 2002), MEDLINE (1966 to January 7, 2002), BIOSIS (1969 to January 7, 2002), CHEMICAL ABSTRACTS (1967 to January 7, 2002).

Bristol-Myers Squibb performed searches in the USA using these search terms: ARIPIPRAZOLE, OPC-14597, OPC14597, OPC-31, OPC31, 129722-12-9 (CAS Registry #), 156680-99-8 (CAS Registry #). The databases and dates searched for online bibliographic references available as of 2 January 2002 were: ADIS R&D Insight, MEDLINE (1958 TO January 2, 2002), CAPLUS/Chemical Abstracts (1907 TO January 2, 2002), EMBASE/EMBASE ALERTS (1974 TO January 2, 2002), BIOSIS/Biological abstracts (1969 TO January 2, 2002), SCISEARCH/Science Citation Index (1974 TO January 2, 2002), DRUGU/Derwent Drug File (1983 TO January 2, 2002), LIFESCI/Life Sciences Collection (1978 TO January 2, 2002), TOXCENTER (1947 TO January 2, 2002), IPA/International Pharmaceutical Abstracts (1970 to January 2, 2002), JICSTE/Japanese Information Center (1985 TO January 2, 2002).

In addition to these sources, abstracts and posters referring to aripiprazole presented at scientific meetings were included in the bibliography. A total of 161

literature references were submitted, including one article that has been submitted for publication.

Three physicians warranted that they had reviewed these articles in detail with respect to safety data relevant to aripiprazole and determined that this literature contains no findings that would adversely affect conclusions about safety contained in NDA 21-436.[6]

In addition, I reviewed the references by title only and found no titles suggesting significant adverse events associated with aripiprazole administration.

### 3. Postmarketing Experience

Aripiprazole has not been marketed.

## V. Clinical Review Methods

### A. Clinical Review Staff and Responsibilities

The clinical review of this NDA was a joint effort between two reviewers: Robert Harris, M.D., Ph.D., of the Neurology Group, and Gregory Dubitsky, M.D., of the Psychiatry Group.

Dr. Harris was responsible for reviewing the clinical safety data and writing sections IV and VII of this document. In addition, he reviewed and prepared comments on the clinical safety sections of the sponsor's proposed labeling (i.e., Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage and Administration).

The remainder of the clinical review and this document was the responsibility of Dr. Dubitsky. Additionally, Dr. Dubitsky served as a mentor to Dr. Harris in carrying out his responsibilities for this NDA.

### B. Items Utilized in the Review

The Division File for ——— was consulted in preparing this document.

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[6] These physicians were: Manabu Yamamura, M.D., Ph.D., and Joy Parris, M.D., both of Otsuka; and Allan Safferman, M.D., of Bristol-Myers Squibb.

Items from the NDA that were examined during the course of this review are depicted in **Appendix V-1**. This review was conducted primarily from documents located in the CDER Electronic Document Room (EDR) under NDA 21-436.

**C. Specific Methods Used to Evaluate Data Quality**

The Division of Scientific Investigations (DSI) inspected a total of 4 clinical sites from 3 of the key efficacy studies in this NDA. Results are described in section II.F of this review.

Dr. Harris conducted an audit of safety data by comparing Case Report Forms (CRF's), Narrative Summaries, and adverse event line listings for consistency of adverse event information across these three documents in a random sample of 39 patients. Also, Dr. Dubitsky audited the CRF's of 10 other randomly selected patients who dropped out for reasons other than adverse experiences to determine if any of these patients actually discontinued treatment for an adverse event. Results are described in section VII.D of this review.

**D. Adherence to Accepted Ethical Standards**

The sponsor indicates that all clinical studies followed Good Clinical Practices (GCP) guidelines.[7] Also, Otsuka certifies that, to the best of its knowledge, information, and belief, it had not and would not use the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

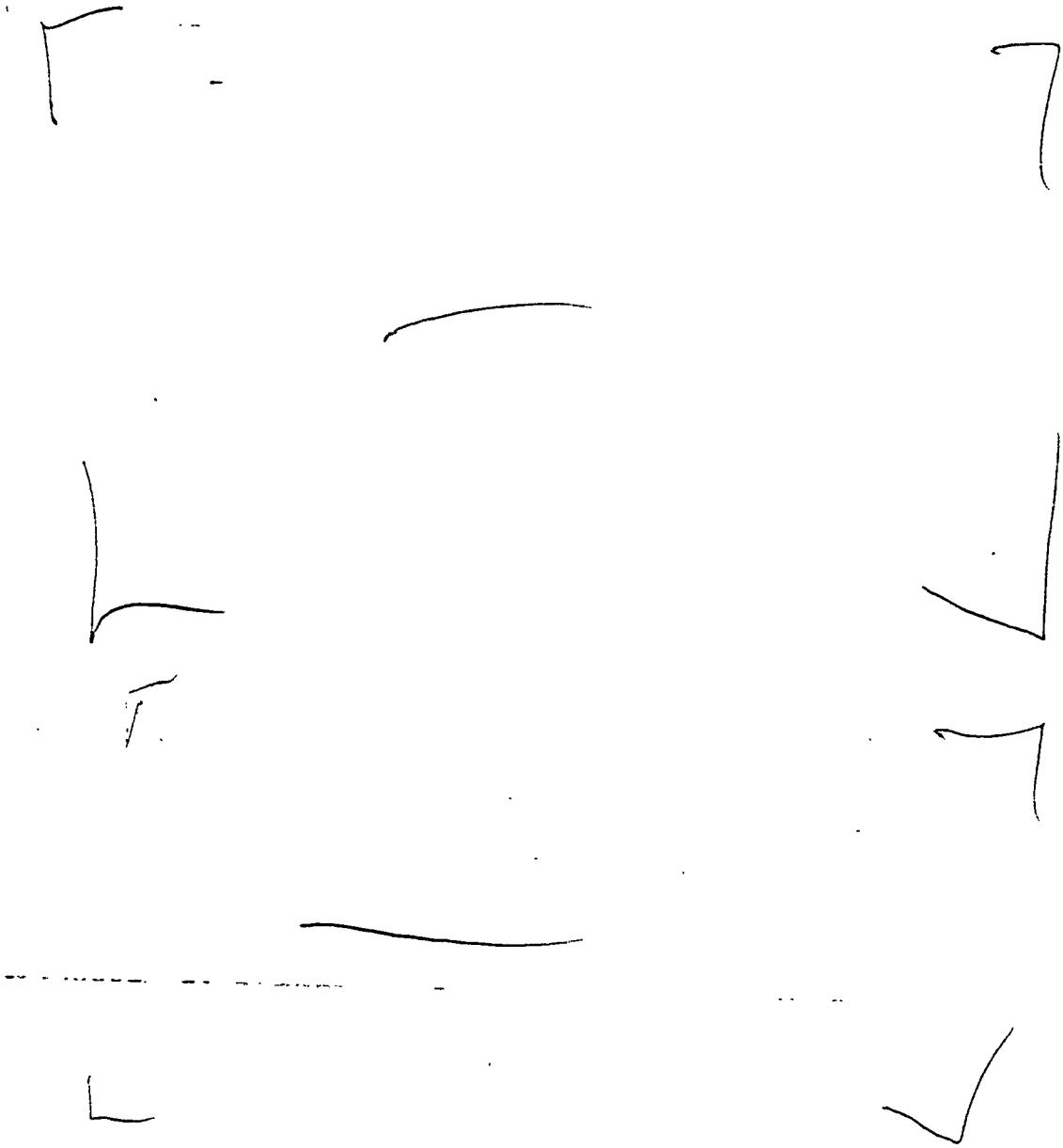
**E. Evaluation of Financial Disclosure**

For purposes of this NDA, there are three trials that are considered "covered clinical studies" in accordance with 21 CFR 54.2(e): 97201, 97202, and 138001.

Among the clinical investigators in these studies, two were identified by Otsuka and BMS as having financial arrangements that require disclosure:

1.

[7] See page 13 of the NDA Application Summary.



## VI. Integrated Review of Efficacy

### A. Overview of Studies Pertinent to Efficacy

The aripiprazole acute efficacy program consists of two Phase 2 trials (93202 and 94202) and three Phase 3 trials (97201, 97202, and 138001). The Phase 2 studies are considered supportive and the Phase 3 studies are considered pivotal by the sponsor.

All five trials were multicenter, randomized, double-blind, and placebo-controlled. Duration and dosing information for these studies is summarized in **Table VI-1** below.

**TABLE VI-1:**
**ADEQUATE AND WELL-CONTROLLED EFFICACY TRIALS**

| Trial | Duration (weeks) | Dosing Regimen | Treatment:Dose(mg/day) |
|---|---|---|---|
| 93202 | 4 | Ascending | Aripiprazole: 30<br>Haloperidol: 20 |
| 94202 | 4 | Fixed | Aripiprazole: 2/10/30<br>Haloperidol: 10 |
| 97201 | 4 | Fixed | Aripiprazole: 15/30<br>Haloperidol: 10 |
| 97202 | 4 | Fixed | Aripiprazole: 20/30<br>Risperidone: 6 |
| 138001 | 6 | Fixed | Aripiprazole: 10/15/20 |

All were conducted in hospitalized patients. Four of the five were performed in the U.S.; the fifth trial (138001) was conducted in the U.S. and Canada.

Four longer-term trials were submitted in the original NDA submission (98217, 98304, 97301, and 98213). None were placebo-controlled or intended to show superiority over an active control agent. Thus, these studies are not capable of providing convincing evidence of efficacy and they will not be discussed further in this review.

## B. Adequate and Well-Controlled Efficacy Trials

### 1. Study 93202

Investigators/Sites

This study was conducted at 10 centers. Investigators are listed in **Appendix VI-1**. There were two additional centers (01 and 03) that did not enroll any patients.

Objectives

The primary objective was to evaluate the efficacy and tolerability of OPC-14597 (a.k.a. aripiprazole) in the treatment of acute schizophrenia.

Secondary objectives were:

- evaluate the effective dose range.
- evaluate relative effect on positive versus negative symptoms.
- assess the pharmacokinetics of OPC-14597 in schizophrenic patients.
- compare the effects of OPC-14597 and haloperidol on serum prolactin in schizophrenic patients.

Patient Sample

Patients were male or female inpatients, between 18 and 65 years old, and had a DSM-III-R diagnosis of schizophrenia with an acute relapse. They must have had a BPRS total score of at least 30 with a score of at least 4 (moderately severe) on two of the four positive symptom items (i.e., conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content). Also, there must have been evidence of a previous response to antipsychotic medication. Patients with more than moderate motor symptoms, as measured by the Simpson-Angus Scale, Abnormal Involuntary Movements Scale, and Barnes Akathisia Scale, were excluded. Other exclusion criteria included:

- primary diagnosis other than schizophrenia.
- substance dependence within the past 2 months.
- cardiac patients for whom hypotension could be hazardous.
- acute or unstable medical condition.

Design

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group, inpatient study. Patients underwent a 3-7 day placebo washout. Eligible patients were then randomized to either OPC-14597, placebo, or haloperidol.

This was the first placebo-controlled study with OPC-14597 in schizophrenia in the U.S. The protocol dosing schedule was amended several times based on information from Phase 1 PK studies. The final dosing schedule is depicted below.

| TABLE VI-2: FINAL DOSING SCHEDULE STUDY 93202 | | |
|---|---|---|
| **Study Days** | **OPC-14597 (dose in mg/day)** | **Haloperidol (dose in mg/day)** |
| 1,2 | 5 | 5 |
| 3,4 | 10 | 10 |
| 5,6 | 15 | 15 |
| 7-12 | 20 | 20 |
| 13-28 | 30 | 20 |

All study drugs were administered once daily after breakfast.

Analysis

Primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population at week 4 (for the last observation carried forward or LOCF dataset) and at each week (for the observed cases or OC dataset). The ITT for efficacy consisted of all patients who had a baseline and a post-baseline measurement of efficacy.

By protocol, there were two primary efficacy variables:

- change from baseline in the BPRS total score and
- the proportion of patients having improved by at least one point on the CGI-Severity scale.

The protocol indicated that changes from baseline in continuous variables and categorical outcomes would be analyzed using 1) Wilcoxon's test and 2) Fisher's exact test or chi-square test, respectively. After completion of the study, the sponsor had decided to utilize 1) ANCOVA and 2) the Cochran-Mantel-Haenszel test, respectively, for the primary analyses since these were considered the industry standards at that timepoint. Results using these latter methods were presented in the study report. Nonetheless, after this discrepancy was noted by both the FDA clinical and statistical reviewers, analyses using the protocol-specified methods were requested by the Agency. The results presented below are based on the protocol-specified analyses.

Another important issue in the review of this trial was the fact that neither the protocol nor any protocol amendments provided for multiplicity adjustment given that two efficacy variables had been designated as primary. Generally, in such a case, both variables must be positive at an alpha of 0.05 for the study to be considered positive. Again, the efficacy results are discussed below in light of this adjustment.

There was one interim analysis of the primary efficacy variables conducted when 50% of the patients had completed 4 weeks of treatment. Since there was no option for early termination of the trial and no change in the conduct of the study based on the interim results, no adjustment to the nominal p-values was made.

Baseline Demographics

Baseline demographic characteristics are summarized in **Appendix VI-2**. Most of the patients in each treatment group were male. Female patients were slightly older than the male patients in the OPC-14597 and placebo groups. Most patients were Caucasian or Black.

Baseline Severity of Illness

Baseline BPRS total scores and CGI-severity scores, shown in **Appendix VI-3**, were roughly comparable among the three treatment groups.

Patient Disposition

The enumeration of patients by disposition is displayed in **Appendix VI-4**.

Overall, slightly more than half (53/103 or 51.5%) of all randomized patients completed the trial. However, there were appreciable differences in completion rates between the active drug and the placebo groups: 61.8% of OPC-14597 patients, 58.8% of haloperidol patients, and only 34.3% of placebo patients completed the study.

The most common reasons for dropout in the active drug groups were withdrawn consent and lack of response to study drug. In the placebo group, withdrawn consent, marked deterioration in clinical status, and lack of response to study drug were most common.

An enumeration of patients by the number of study days completed is displayed in **Appendix VI-5**. At least 70% of the randomized patients in each treatment group completed 15-21 days in the study.

Concomitant Medications

Treatment with concomitant psychotropic medication was prohibited with the exception of lorazepam (up to 10 mg/day) for emergent anxiety or insomnia. There were no substantial differences across the three treatment groups in terms of the percentage of patients using lorazepam or the average dose (mg) used per day during double-blind treatment (see Table 7.4.9-1 in the study report). It is notable that four patients in the OPC-14597 group, one patient in the placebo group, and one patient in the haloperidol group took concomitant haloperidol. All but one of these patients took concomitant haloperidol for only one day. The remaining patient (93202-9-100) began haloperidol treatment on the final day of study drug.

Moderate to severe extrapyramidal symptoms, akathisia, or dystonia could be treated with benztropine at a dose up to 6 mg/day. The percentage of patients administered benztropine was considerably less in the OPC-14597 and placebo groups compared to the haloperidol group during double-blind therapy (17.6%, 28.6%, and 55.9%, respectively).

Efficacy Results

At our request, the sponsor analyzed the two primary efficacy variables utilizing the protocol-specified methods at the final visit (LOCF)(OC results were not reported). Analyses of secondary variables were not provided. Results were forwarded in a 3-17-02 E-Mail to the FDA Project Manager, Steve Hardeman.

Findings based on the mean change in the BPRS total score are summarized in **Appendix VI-6**. Baseline scores were compared using ANCOVA. Week 4 changes were compared using Wilcoxon's test.

OPC-14597 was numerically superior to placebo, demonstrating a decrease of 7.2 points in the BPRS total score compared to a decrease of 2.1 points in the placebo

group. However, the intergroup difference was not statistically significant (p=0.173). Haloperidol did demonstrate superiority over placebo, with a decrease of 8.1 points (p=0.010).

Results based on the proportion of patients with at least one point of improvement on the CGI-Severity scale are summarized in **Appendix VI-7**. The proportions meeting this criteria at weeks 4 were compared using the Chi-Square test as well as the Fisher's exact test.

In the OPC-14597 group, 42.4% of the LOCF population had at least one point improvement on the CGI-Severity scale; only 20% of the placebo group met this criteria. The difference between OPC-14597 and placebo was statistically significant using the Chi-Square test (p=0.045) but not using the Fisher's exact test (p=0.066). Haloperidol was statistically superior to placebo using both tests (p=0.003 and 0.005, respectively).

Conclusions

A finding of efficacy in this trial with two primary outcome variables requires statistical superiority over placebo for each variable at an alpha level of 0.05.

OPC-14597 failed to demonstrate statistical superiority over placebo on the BPRS total score. Efficacy results based on the percentage of patients with at least one point improvement on the CGI-Severity scale were analysis-dependent. Thus, this study failed to demonstrate the efficacy of OPC-14597.

On the other hand, haloperidol demonstrated clear evidence of efficacy.

In terms of OPC-14597, study 93202 must be considered negative.

**2. Study 94202**

Investigators/Sites

This study was conducted at the 22 centers listed in **Appendix VI-8**. The investigator at center 003 — — was disqualified due to allegations of research misconduct and conviction on criminal charges. Therefore,

efficacy data from this center were excluded from analyses discussed below. An additional center (015) did not enroll any patients.

Objectives

The primary outcome of this study was to determine an optimal dose of OPC-14597 (a.k.a. aripiprazole) for the treatment of acute schizophrenia.

Patient Sample

Amendment #2 to the original protocol provided for the enrollment of 300 patients.

At screening, patients must have been in the age range 18-65 with a primary DSM-IV diagnosis of schizophrenia, in acute relapse, and hospitalized. Also required was a BPRS total score of at least 36 and a score of at least 4 ("moderate") on any two of the following four items: hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness. Antipsychotic medication must not have been taken for at least 72 hours prior to randomization (generally 4 weeks for a long-acting agent).

Patients experiencing their first episode of schizophrenia or with a history of being refractory to conventional antipsychotics were excluded at screening. Also, any of the following were exclusionary at this visit: moderate to severe EPS, dyskinesia, or akathisia; substance abuse or dependence, cardiac disease for whom hypotension could be hazardous, cardiac conduction defects, an acute or unstable medical condition, pregnant or lactating females, and females not using adequate contraception.

At baseline (randomization), patients were assessed again with respect to the above BPRS criteria, antipsychotic drug use, and motor symptoms.

Design

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group, dose-ranging inpatient study.

Patients underwent a 3-7 day placebo washout period. Then, eligible patients were randomized to one of three fixed

doses of OPC-14597 (2, 10, or 30 mg/day), haloperidol (10 mg/day), or placebo. The dosing schedule is depicted in **Table VI-3** below. The dose of study drug could not be modified during the trial.

**TABLE VI-3:**
**DOSING SCHEDULE**
**STUDY 94202**

| Study Days | OPC-14597 | | | Halop. |
|---|---|---|---|---|
| | 2 mg/day | 10 mg/day | 30 mg/day | |
| 1 | 1 | 5 | 15 | 5 |
| 2 | 2 | 10 | 30 | 5 |
| 3-28 | 2 | 10 | 30 | 10 |

All study medication was administered once daily after breakfast. OPC-14597 was supplied a white tablets in dose levels of 1, 5, and 15mg. Haloperidol was supplied a overencapsulated 5mg tablets in brown opaque gelatin capsules in dose levels of 5 and 10mg. Placebo was provided as tablets that matched the OPC-14597 tablets and as capsules that matched the haloperidol capsules. Patients in all treatment groups received some combination of tablets and capsules.

Analysis

Primary and secondary efficacy analyses were performed on the efficacy intent-to-treat (ITT) population, defined in the study report as consisting of all patients who had a baseline and a post-baseline measurement of efficacy regardless of whether the patient received medication or had a protocol violation.[8]

By protocol, there were two primary efficacy variables:

- the change from baseline to last visit in the BPRS core score (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and
- the CGI rating of improvement at last visit.

The primary efficacy analysis was ANCOVA, with terms for treatment and center and, for the BPRS variable, baseline score as covariate. Amendment #2 to the protocol was

[8] The study protocol and amendments failed to specifically define an intent-to-treat population. Hence, the definition in the study report will be used for purposes of this review.

intended specify the use of Dunnett's procedure to adjust for multiplicity based on the pairwise comparison of each of the three dose groups to placebo.[9]

Neither the protocol nor any protocol amendments provided for multiplicity adjustment given that two efficacy variables had been designated as primary. In this case, it is presumed that, at each dose level, both variables must be positive at 0.017 for superiority over placebo to be declared at that dose. The efficacy results are discussed below in light of this adjustment.

Additionally, for reasons mentioned above, the discussion below will focus on analyses which excluded data from center 003.

Baseline Demographics

**Appendix VI-9** displays the demographic characteristics of the patient sample at baseline. Most patients were male. Mean ages among the five treatment groups were in the late 30's to early 40's. Most patients were white except among males in the OPC-14597 30mg group, where Blacks outnumbered Whites. Overall, there were no notable demographic differences between treatment groups.

Baseline Severity of Illness

**Appendix VI-10** depicts the mean BPRS core scores and CGI-severity scores at baseline. There were no major differences between treatment groups.

Patient Disposition

**Appendix VI-11** displays the disposition of study patients by treatment group. Dropout rates ranged from 33% in the OPC-14597 30mg group to 55% in the placebo group. A few patients in the OPC-14597 2mg and 10mg and haloperidol groups dropped out due to a marked deterioration in clinical status. Several patients in each group (except the OPC-14597 10mg group) dropped out due to lack of response; this was the most common reason for dropout in

[9] The actual amendment indicates that pairwise comparisons would be performed using the Dunn test with an alpha of 0.017. A 3-14-02 E-Mail from the sponsor states that this was an error and that ANCOVA, followed by Dunnett's correction, was actually intended and used for the presented analyses.

the placebo group. About an equal percentage of patients dropped out due to adverse events in the low- and high-dose OPC-14597 and haloperidol groups. Four OPC-14597 patients dropped out for "other" reasons: under-treatment due to a date error, administrative reason, unauthorized absence from the hospital, and a departure from the inpatient unit.

An enumeration of patients by the number of study days completed is displayed in **Appendix VI-12**. At least 70% of the OPC-14597 patients completed 15-21 days in the study.

Concomitant Medications

Treatment with concomitant psychotropic medication was prohibited with the exception of lorazepam (up to 10 mg/day) for emergent anxiety or insomnia. Lorazepam was, in fact, the most commonly used concomitant medication: over 80% of patients in each treatment group took lorazepam at some time during double-blind treatment. There were no large differences between groups in the percentage of patients who took lorazepam. An appreciable impact of this usage on the core symptoms of psychosis seems unlikely but, to the extent that such an influence occurred, it would have blurred distinctions between the treatment groups.

During double-blind treatment, several patients received concomitant antipsychotic agents (fluphenazine, haloperidol, perphenazine, risperidone, thiothixene, and trifluoperazine).[10] This use occurred in small numbers of patients and was distributed among all treatment groups but most commonly in the placebo group. This may have biased results against the active drug groups.

Extrapyramidal symptoms, akathisia, or dystonia could be treated with benztropine at a dose up to 6 mg/day. The percentages of patients administered benztropine in the OPC-14597 groups were dose-related: 17%, 27%, and 34% in the 2, 10, and 30mg groups, respectively. In the haloperidol group, 44% received benztropine. In the placebo group, 30% did so.

[10] See Appendix 1B-1.2 of the study report.

Efficacy Results

Efficacy findings based on the change in the BPRS core score and the CGI-improvement item are displayed in **Appendix VI-13** and **Appendix VI-14**, respectively.

On the BPRS core score and prior to Dunnett's correction, OPC-14597 was not statistically superior to placebo at any dose at weeks 2, 3, or 4 using the observed cases dataset nor at week 4 with the LOCF dataset. Haloperidol was barely superior to placebo only at week 4 with the LOCF dataset ($p=0.0495$).

On the CGI-improvement item, OPC-14597 was not superior to placebo with the observed cases dataset at weeks 2, 3, or 4 prior to correction. With the LOCF dataset at week 4, superiority of OPC-14597 over placebo was demonstrated ($p=0.0055$). This significance was maintained following Dunnett's correction ($\alpha=0.017$). Haloperidol was not superior to placebo.

Conclusions

OPC-14597 demonstrated superiority over placebo for 30mg group on only one of the two primary efficacy variables (CGI-improvement item). Haloperidol was not superior to placebo.

Hence, study 94202 must be considered a failed study.

**3. Study 97201**

Investigators/Sites

This study involved 36 centers in the U.S. Principal investigators are listed in **Appendix VI-15**. (Gaps in the sequence of center numbering are due to centers that failed to enroll any patients.)

Objectives

The primary objective of this study was to compare the safety and efficacy of 15mg and 30mg aripiprazole doses to placebo in the treatment of acute psychosis in patients with schizophrenia or schizoaffective disorder.

Patient Sample

A total of 502 patients, age 18-65, with DSM-IV schizophrenia or schizoaffective disorder were screened. The following were important inclusion criteria:

- acute relapse of either schizophrenia or schizoaffective disorder at screening.
- generally, no treatment with a long-acting neuroleptic within one treatment cycle plus one week prior to randomization.
- at both screening and the end of placebo washout, PANSS total score of at least 60 and a score of at least 4 (moderate symptomatology) on any two of the four items of the PANSS psychotic subscale (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness).
- randomization within 4 weeks after starting treatment for the current episode.
- response to previously administered antipsychotic agents.
- females must not be pregnant or lactating; women of childbearing potential must agree to use acceptable contraception.

Exclusionary criteria included the following:

- first episode of schizophrenia or schizoaffective disorder.
- psychiatric diagnosis other than schizophrenia or schizoaffective disorder that required pharmacotherapy.
- a neurological condition.
- an acute or unstable medical condition requiring pharmacotherapy
- substance dependence within one month of the study.
- potential need for medications that could cause unwanted interactions or confound the analysis of efficacy, including carbamazepine, valproic acid, and lithium.
- potential need for any agent that is a potent inhibitor of CYP2D6.
- positive drug screen for drugs of abuse.

Design

This was a 4 week, randomized, double-blind, placebo- and haloperidol-controlled, parallel group, inpatient study.

After a minimum 5 day placebo washout, eligible patients were randomized to one of four treatment groups: aripiprazole 15mg/day, aripiprazole 30mg/day, haloperidol 10mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment once daily in the morning. Patients who could not tolerate study medication were dropped out. Visual inspection was performed after dose administration to ensure ingestion.

Study medication was supplied as placebo capsules and tablets, aripiprazole 15mg tablets, and haloperidol 10mg capsules (each containing two 5mg tablets). All patients received 2 tablets and one capsule each morning. All tablets and all capsules were matched in appearance to maintain the blind.

Analysis

Primary efficacy analyses were performed on the intent-to-treat (ITT) population, defined in the study protocol as all patients having a baseline and a post-baseline observation regardless of whether the patient received medication.

By protocol, there were three primary efficacy variables:

- change from baseline in the PANSS total score.
- change from baseline in the PANSS positive subscale.
- change from baseline in the CGI-severity score.

The primary analysis was ANCOVA, with terms for treatment, center, and treatment-by-center interaction, with baseline score as covariate for the LOCF dataset. If the treatment-by-center interaction was non-significant at the 0.10 level, it was to be excluded from the model. All Observed-Cases analyses included only treatment and baseline values in the model; center effect was not included due to the large number of small centers in this trial.

By protocol, treatment comparisons would be done using a step-down procedure: aripiprazole 30mg vs. placebo would first be tested at a 2-tailed 0.05 level; then, if the null hypothesis was rejected, aripiprazole 15mg vs. placebo would be tested at a 2-tailed 0.05 level.

The protocol did not provide for multiplicity adjustment given that three efficacy variables had been designated as

primary. In such a case, generally all three variables must be positive at an alpha of 0.05 for the study to be considered positive. The efficacy results are discussed below in light of this adjustment.

An internal audit conducted by the sponsor revealed that data generated at centers 007 and 011 could not be validated. Thus, the sponsor conducted an additional analysis of the mean change from baseline in the PANSS total score which excluded the 16 patients randomized at center 007 and the 3 patients randomized at center 011.

Baseline Demographics

**Appendix VI-16** displays the demographic characteristics of the randomized patient sample at baseline. Most patients were male. Mean ages were in the late 30's. Most patients were white; in the placebo group, almost half were non-white. Overall, there were no notable demographic differences between treatment groups.

Of the 401 patients in the efficacy ITT, 276 (69%) were diagnosed with schizophrenia; the remaining patients had a diagnosis of schizoaffective disorder. The two aripiprazole dose groups and the placebo groups had approximately the same percentage of schizophrenic patients (about 72%). The haloperidol group had a smaller proportion of schizophrenic patients (60%).

Baseline Severity of Illness

**Appendix VI-17** depicts the mean PANSS total scores and CGI-severity scores at baseline. Differences between the groups were extremely small.

Patient Disposition

**Appendix VI-18** enumerates the 414 randomized patients by disposition. Dropout rates ranged from 33% in the aripiprazole 15mg group to 45% in the placebo group. The percentage of dropouts due to adverse events was highest in the placebo group (16%). Dropout rates for adverse experiences for the two aripiprazole dose groups were almost identical (8-9%), despite a two-fold difference in dose. A relatively large proportion of patients (14% overall) dropped out after withdrawing consent. About 14% of all patients dropped out due to poor therapeutic

response, with the highest percentage in the aripiprazole 30mg group and the lowest in the 15mg group.

An enumeration of patients in-study by week is displayed in **Appendix VI-19**. At least 70% of the aripiprazole and haloperidol patients remained in-study at the week 3 visit.

Concomitant Medications

By protocol, lorazepam and other benzodiazepines were permitted during the study for any reason and at any dose deemed appropriate for the patient's management. If judged necessary, extrapyramidal symptoms could be treated with benztropine at doses not to exceed 6 mg/day. The severity of EPS was to be documented on the Simpson-Angus Scale and Barnes Akathisia Scale prior to first-time treatment with benztropine.

Anxiolytics were the most frequently used concomitant medication in this trial: approximately 80% of patients in each of the four treatment groups received a concomitant anxiolytic agent. Also, about 25% of patients in each group received a sedative/hypnotic agent.

A number of patients received a concomitant antipsychotic drug, most frequently in the placebo group (N=9) and haloperidol group (N=6). Five patients in the aripiprazole 15mg group and one aripiprazole 30mg patient received another antipsychotic. The degree to which this usage influenced the efficacy results is unknown. Based on the relatively larger number of placebo patients with such use, it seems more likely that this treatment would bias the results against aripiprazole rather than in favor of aripiprazole.

Efficacy Results

Efficacy results based on the changes from baseline in the PANSS total score, PANSS positive subscale, and CGI-severity of illness score are summarized in **Appendix VI-20**, **Appendix VI-21**, and **Appendix VI-22**, respectively.

With respect to the protocol-specified first step-down comparison (aripiprazole 30mg vs. placebo), aripiprazole

was superior to placebo at week 4 on all three variables in both OC and LOCF analyses at an alpha of 0.05.[11]

Similarly, regarding the second step-down comparison (aripiprazole 15mg vs. placebo), aripiprazole was superior to placebo at week 4 on all primary variables in both OC and LOCF analyses at an alpha of 0.05 (all p-values were ≤0.001).

An examination of OC results at earlier visits revealed less consistency: for both aripiprazole doses, week 2 results demonstrated superiority of drug over placebo. At week 3, however, most differences became non-significant; this appears to be due to large improvements in the placebo group at week 3, with smaller degrees of improvement from week 3 to week 4 in that group.

There is a pattern for dose-response that is consistent across all three primary efficacy variables: the mean changes from baseline at week 4 in the LOCF analyses are greater for the 15mg dose group than in the 30mg dose group. This is also true in the OC analyses. These data suggest that there is no therapeutic advantage of aripiprazole 30 mg/day over 15 mg/day.

Since this study enrolled both schizophrenic and schizoaffective patients, I examined the primary efficacy results (LOCF) based on the schizophrenia and schizoaffective subsets separately.[12] A comparison of the placebo-adjusted mean changes from baseline between the two diagnostic subsets revealed a similar degree of improvement on all three primary variables in both aripiprazole dose groups.

Efficacy analyses that excluded the centers where data could not be validated (centers 007 and 011) were provided by the sponsor for the change in the PANSS total score.[13] A comparison of the results with and without these two centers revealed no important differences. The FDA statistical reviewer, Dr. Yeh-Fong Chen, analyzed the other

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[11] For the comparison based on the CGI-severity score in the OC analysis at week 4, I consider the borderline p-value of 0.053 to be statistically significant.

[12] The results from the schizophrenia subset may be found on pages 107, 115, and 123 of the study report. Results from the schizoaffective subset may be found in a 5-15-02 submission from the sponsor.

[13] These results may be viewed on pages 207 and 208 of the study report.

two primary variables after excluding these two centers. She found the results to be consistent with those based on all centers.[14]

Changes in the PANSS negative subscale, one of the secondary variables in this study, demonstrated efficacy for the 15mg aripiprazole dose but not for the 30mg dose.[15] Although both doses were numerically superior to placebo, the mean drug/placebo difference for the lower dose was considerably larger than that for the higher dose (-2.4 vs. -1.1 in the LOCF analysis at week 4). To a small degree, this might be explained by slight worsening of Parkinsonian symptoms in the 30mg vs. the 15mg group as suggested by mean changes in Simpson-Angus Scale scores at endpoint: -0.3 for the 15mg patients and +0.2 for the 30mg patients.[16]

Conclusions

Study 97201 adequately demonstrates the efficacy of aripiprazole 15 mg/day and 30 mg/day in the treatment of psychosis among patients with schizophrenia. Data from this trial suggest no therapeutic advantage of the 30mg over the 15mg dose.

**4. Study 97202**

Investigators/Sites

This study was conducted at 40 centers in the U.S. Principal investigators are listed in **Appendix VI-23**.

Objectives

The objective of this study was to compare the safety and efficacy of aripiprazole 20mg and 30mg versus placebo in the treatment of acute psychosis in patients with schizophrenia or schizoaffective disorder.

Patient Sample

A total of 487 patients, age 18-65, with DSM-IV schizophrenia or schizoaffective disorder were screened. The following were important inclusion criteria:

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[14] Dr. Chen communicated her findings to me in a 4-22-02 E-Mail.
[15] Results are found on pages 126 and 127 of the study report.
[16] Negative change scores indicate improvement in Parkinsonism.

- acute relapse of either schizophrenia or schizoaffective disorder at screening.
- generally, no treatment with a long-acting neuroleptic within one treatment cycle plus one week prior to randomization.
- at both screening and the end of placebo washout, PANSS total score of at least 60 and a score of at least 4 (moderate symptomatology) on any two of the four items of the PANSS psychotic subscale (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness).
- randomization within 4 weeks after starting treatment for the current episode.
- response to previously administered antipsychotic agents.
- females must not be pregnant or lactating; women of childbearing potential must agree to use acceptable contraception.

Exclusionary criteria included the following:

- first episode of schizophrenia or schizoaffective disorder.
- psychiatric diagnosis other than schizophrenia or schizoaffective disorder that required pharmacotherapy.
- a neurological condition.
- an acute or unstable medical condition requiring pharmacotherapy.
- substance dependence within one month of the study.
- potential need for medications that could cause unwanted interactions or confound the analysis of efficacy, including carbamazepine, valproic acid, and lithium.
- potential need for any agent that is a potent inhibitor of CYP2D6.
- positive drug screen for drugs of abuse.

Design

This was a 4-week, randomized, double-blind, placebo- and risperidone-controlled, parallel group, inpatient study.

After a minimum 5 day placebo washout, eligible patients were randomized to one of four treatment groups: aripiprazole 20mg/day, aripiprazole 30mg/day, risperidone 6mg/day, or placebo.

Study medication was administered twice daily. Study medication was supplied as placebo tablets, encapsulated placebo tablets, aripiprazole 10mg and 15mg tablets, and encapsulated risperidone 1mg, 2mg, and 3mg tablets. All patients received two tablets and one capsule in the morning after breakfast and one capsule after the evening meal.

Aripiprazole was given as a full fixed dose once daily each morning from the first day of treatment; evening doses for aripiprazole group patients consisted of placebo.

Risperidone was titrated as follows: 1mg BID on day 1, 2mg BID on day 2, and 3mg BID on day 3 and thereafter. Dose modifications were not allowed and patients who could not tolerate study medication were dropped out. Visual inspection was performed after dose administration to ensure ingestion.

Analysis

Primary efficacy analyses were performed on the efficacy intent-to-treat sample, defined in the study protocol as all patients having a baseline and post-baseline observation regardless of whether study medication was received.

By protocol, there were three primary efficacy variables:

- change from baseline in the PANSS total score.
- change from baseline in the PANSS positive subscale.
- change from baseline in the CGI-severity score.

The primary analysis was ANCOVA, with terms for treatment, center, and treatment-by-center interaction, with baseline score as covariate. If the treatment-by-center interaction was non-significant at the 0.10 level, it was to be excluded from the model. All Observed-Cases analyses included only treatment and baseline values in the model; center effect was not included due to the large number of small centers in this trial.

By protocol, treatment comparisons were to be performed using a step-down procedure: aripiprazole 30mg vs. placebo would first be tested at a 2-tailed 0.05 level; then, if the null hypothesis was rejected, aripiprazole 20mg vs. placebo would be tested at a 2-tailed 0.05 level.

The protocol did not provide for multiplicity adjustment given that three efficacy variables had been designated as primary. Thus, all three variables must be positive at an alpha of 0.05 for the study to be considered positive. The efficacy results are discussed below in light of this adjustment.

Baseline Demographics

**Appendix VI-24** displays the demographic characteristics of the randomized patient sample at baseline. Most patients were male. Mean ages were in the range of 38 to 40 years old and most patients were white. Overall, there were no major demographic differences among treatment groups.

Of the 392 patients in the efficacy ITT, 282 (72%) were diagnosed with schizophrenia; the remaining patients had a diagnosis of schizoaffective disorder. The two aripiprazole dose groups (20mg and 30mg) had a smaller percentage of patients diagnosed with schizophrenia than the placebo and risperidone groups: 66% and 71% versus 76% and 75%, respectively.

Baseline Severity of Illness

**Appendix VI-25** depicts the mean PANSS total scores and CGI-severity scores at baseline. Mean PANSS total scores ranged from 92.6 to 95.7. Mean CGI-severity scores were essentially identical (4.8).

Patient Disposition

**Appendix VI-26** enumerates the 404 randomized patients by disposition. Dropout rates ranged from 34% in the aripiprazole 30mg group to 50% in the placebo group. The percentage of dropouts due to adverse events was highest in the placebo group (17%). A relatively large proportion of patients (12% overall) dropped out after withdrawing consent. The highest percentage of dropouts due to poor clinical response occurred in the placebo group (21%); in the two aripiprazole groups, the percentages of patients dropping out for this reason were comparable.

An enumeration of patients in-study by week is displayed in **Appendix VI-27**. At least 70% of the aripiprazole and placebo patients were in-study at the week 2 visit. By the

week 3 visit, a considerably higher fraction of patients had dropped out of the placebo group compared to the three active drug groups.

Concomitant Medications

By protocol, lorazepam and other benzodiazepines were permitted during the study for any reason and at any dose deemed appropriate for the patient's management. If judged necessary, extrapyramidal symptoms could be treated with benztropine at doses not to exceed 6 mg/day. The severity of EPS was to be documented on the Simpson-Angus Scale and Barnes Akathisia Scale prior to first-time treatment with benztropine.

Anxiolytics were the most frequently used concomitant medication in this trial: about three-fourths of the patients in each of the four treatment groups received a concomitant anxiolytic agent. Also, 20-30% of patients in each group received a concomitant sedative/hypnotic agent.

A total of 10 efficacy ITT patients received a concomitant antipsychotic drug during study treatment and prior to or on the day of the final efficacy assessment (5 patients in the 20mg group, 1 in the 30mg group, 3 in the placebo group, and 1 in the risperidone group). Of the 6 aripiprazole patients, 2 took the concomitant antipsychotic one day prior to the final efficacy assessment; the remaining 4 did not receive the concomitant antipsychotic until the day of the final assessment.[17] Thus, while a significant confounding influence on efficacy cannot be absolutely ruled out, this seems unlikely.

Efficacy Results

Change from baseline data for the PANSS total score, PANSS positive subscale, and CGI-severity of illness score are summarized in **Appendix VI-28**, **Appendix VI-29**, and **Appendix VI-30**, respectively.

With respect to the protocol-specified first step-down comparison (aripiprazole 30mg vs. placebo), aripiprazole was superior to placebo at week 4 on all three variables in the LOCF analyses. However, aripiprazole 30mg was not statistically superior in the OC analyses for any of the

[17] This information is based on a 6-3-02 submission from BMS.

primary variables. It appears that a major contributor to the failure of the OC analyses to demonstrate superiority was the large change from baseline among placebo patients who remained in the study (e.g., -18.2 in the PANSS total score vs. -5.0 in the LOCF analysis). While there also was a larger mean change from baseline in the aripiprazole 30mg group for the OC vs. the LOCF analysis, the difference between the two analyses tended to be even larger in the placebo group. Thus, it seems that the dropout of poorly responding placebo patients biased the OC analyses against aripiprazole.

Similarly, with respect to the second step-down comparison (aripiprazole 20mg vs. placebo), aripiprazole was superior to placebo at week 4 on all primary variables in the LOCF analyses but was superior only for the PANSS positive subscale in the OC analyses. As with the 30mg OC results, the 20mg OC data appears to have been biased by the dropout of poorly responding placebo patients.

An examination of OC results at earlier visits revealed superiority of the 20mg dose over placebo at week 2 on all three primary variables as well as superiority of the 30mg dose on the CGI-severity score at week 2. At that visit, mean changes from baseline in the placebo groups were modest.

Examination of the risperidone vs. placebo comparisons at final visit revealed this same pattern of results: for two of the three primary variables (PANSS total score and positive subscale), the LOCF results were significant but the OC results were non-significant. For the CGI-severity score, both LOCF and OC results were significant but much more robust in the LOCF analysis.

An evaluation of dose-response revealed somewhat mixed results: aripiprazole 20mg was associated with slightly larger mean changes from baseline to week 4 for the PANSS total score and positive subscale (LOCF) compared to the 30mg dose; however, for the CGI-severity score, the 30mg dose was slightly better. None of the differences between the two doses for the three primary variables was large. These data suggest that there may be no therapeutic advantage of aripiprazole 30 mg/day over 20 mg/day.

Since this study enrolled both schizophrenic and schizoaffective patients, I examined the primary efficacy

results (LOCF) based on the schizophrenia and schizoaffective subsets separately.[18] A comparison of the placebo-adjusted mean changes from baseline between the two diagnostic subsets revealed a comparable degree of improvement on all three primary variables in both aripiprazole dose groups.

Changes in the PANSS negative subscale, one of the secondary variables in this study, demonstrated equivalent efficacy for the 20mg and 30mg aripiprazole doses (LOCF).

Conclusions

Study 97202 produced observed cases efficacy results that were biased by the early dropout of large numbers of poorly responding placebo patients. Thus, drug/placebo comparisons in this analysis tended to be non-significant.

On the other hand, the LOCF results clearly demonstrated the superiority of aripiprazole 20 mg/day and 30 mg/day over placebo on all three primary efficacy variables.

On the whole, this trial is felt to provide evidence of efficacy for both doses of aripiprazole studied in patients with schizophrenia. As with study 97201, data from this trial suggest no therapeutic advantage of the 30mg over the 20mg dose.

**5. Study 138001**

Investigators/Sites

This study was conducted at 57 centers, 53 in the U.S. and 4 in Canada. Principal investigators are listed in **Appendix VI-31**.

Objectives

This trial evaluated the efficacy of three fixed doses of aripiprazole versus placebo in the treatment of acutely relapsed schizophrenic patients. The secondary objective was to evaluate the safety of this treatment.

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[18] The results from the schizophrenia subset may be found on pages 104, 112, and 120 of the study report. Results from the schizoaffective subset may be found in a 5-15-02 submission from the sponsor.